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Insulin in Amyotrophic Lateral Sclerosis: Impairment, Tests and Treatment

Ari Rappoport
The Hebrew University of Jerusalem, Israel
ari.rappoport@mail.huji.ac.il

Abstract

Background. Amyotrophic Lateral Sclerosis (ALS) is a devastating disease involving motor neuron degeneration. The few drugs approved for treatment have at most a marginal benefit, and death usually occurs 2-5 years after diagnosis.

Methods. A thorough manual examination of the relevant literature, covering over 35,000 papers.

Results. Two major phenomena generally not recognized by clinicians were found. First, insulin signaling is impaired in ALS even in patients not diagnosed with diabetes (DB). Almost all studies that have explicitly tested insulin function in non-DB ALS patients using glucose tolerance tests (18 out of 21, 1964-2022, different groups) have found it to be impaired. Second, there is strong evidence for excessive insulin-independent glucose uptake (IIGU) in ALS. In addition, (i) early/late diabetes are associated with increased/decreased risk, respectively; (ii) insulin-based diabetes drugs are protective in ALS in large retrospective human studies; and (iii) strong animal and human evidence shows that insulin opposes all of the major pathological processes in ALS.

Conclusion. Most ALS patients have insulin impairment, yet this is commonly not diagnosed, likely because excessive IIGU normalizes glucose levels. The impairment promotes disease progression and may be the symptom trigger. Late diabetes is associated with decreased risk because high glucose levels indicate non-excessive IIGU, and because diabetes drugs are protective. Insulin-based treatment (e.g., GLP1 agonists, insulin) is beneficial and can be disease-modifying in ALS and in frontotemporal dementia variants comorbid with ALS. ALS patients should be routinely tested for insulin function and treated if test results are positive.

Keywords. ALS, frontotemporal dementia, insulin, diabetes

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Introduction

ALS is a disease of unknown etiology involving the degeneration of motor neurons (MTNs).[1,2] There are two variants, sporadic ALS (sALS), which affects 80-90% of the patients, and familial ALS (fALS), usually associated with gene mutations. There is strong comorbidity with frontotemporal dementia (FTD), mainly its behavioral variant (bvFTD).[3,4] The few approved treatments have only a marginal benefit,[5–7] and death usually occurs two to five years after diagnosis.

Here I point to a promising immediately available therapy, which, although based on strong existing evidence, is not recognized by the medical community. I highlight wide evidence that insulin function is impaired in a large subset of ALS patients, and explain why it is usually not detected and why insulin-based therapy (insulin itself or drugs promoting its secretion) should provide benefit. The account is supported by wide epidemiological data on the relationship between ALS and diabetes mellitus (DB) and body mass index (BMI), studies showing that DB drugs are associated with decreased ALS risk, imaging and molecular evidence in ALS, and other preclinical results.

Method

An extensive manual examination of the relevant literature has been conducted over several years. Papers were identified via searches of Google Scholar and PubMed between 1950 and November 2022, and references from and citations of relevant articles. The search terms used were ALS, FTD, glucose, insulin, diabetes, AMPK, cellular stress, unfolded protein response, oxidative stress, glutathione, TDP-43, and calcium. Hundreds of thousands of papers were examined, with over 35,000 papers thoroughly read.

Note that although the methodology used is similar to that used for reviews, this paper is not a review. It reports novel results, which are based on previously reported empirical evidence.

Known ALS pathophysiology

The etiology of ALS is not known, but much is known about its pathophysiology. Both sALS and fALS cells show clear cellular stress and stress responses, including endoplasmic reticulum (ER) stress,[8–11] unfolded protein and heat shock responses (UPR, HSR),[12–20] oxidative stress[9,21] with reduced glutathione (GSH)[22,23] and increased lipid peroxidation,[24–30] and immune reactivity.[31,32] Indeed, almost all patients show pathological accumulation of the TDP-43 protein, which is associated with stress responses.[33] ALS cell stress involves excitotoxicity, with much evidence pointing to calcium overload.[34–40] Mitochondria are impaired, with reduced oxidative phosphorylation[9,41–45] and permeability pore opening.[46]

These phenomena are widely recognized and comprise the logical foundation of the drugs approved for ALS and of almost all clinical trials done over the years.[47]

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Insulin is impaired in ALS

A thorough search and examination of the literature revealed that ALS exhibits an additional strong pathophysiology, insulin impairment. Twenty one papers published during the last sixty years have reported the results of explicit glucose tolerance or insulin tests (mainly using the oral glucose tolerance test (OGTT)) in ALS patients who were not previously diagnosed with diabetes. Of these, eighteen reported impaired insulin secretion[48–53] or signaling,[54–65] and one reported an inverse correlation between gluocse disposal rate and disease severity.[66] Only two early papers reported normal glucose tolerance, one using only neurological patients as controls,[67] and one not using controls at all.[68] Another paper found increased plasma and CSF alpha-hydroxybutyrate (a pre-diabetes marker),[69] and another reported insulin resistance (IR) in bvFTD.[70]

In other words, **almost anybody who has ever tested insulin function in ALS has found it to be impaired in patients not previously diagnosed with diabetes** (at the group level). We can conclude that insulin is impaired in a significant subset of ALS patients.

In addition to these results, there are strong epidemiological data pointing to a link between ALS and DB. Studies examining whole-country registers in England, Sweden, Taiwan, and Denmark have shown that early DB (diagnosed before the age of 50 in Sweden and Denmark or 65 in Taiwan) is associated with increased ALS risk.[71–75] In addition, high HbA1c (indicating high blood glucose levels over a time period) is significantly associated with higher ALS mortality.[76]

Indirect support for insulin impairment in ALS comes from BMI data. Low BMI is a known marker of severe insulin impairment (see also below), and pre-onset low BMI is strongly associated with increased risk.[77–85]

These data might suggest that type-2 DB (DB2) would be associated with increased ALS risk. However, there is strong country, regional, and single clinic evidence that late age DB is associated with *decreased* ALS risk,[72,74,75,86–91] delayed onset,[85,92–94] and longer survival.[92,93] We explain this apparent paradox further below.

These results are generally not mentioned at all, or mentioned very little, in relation to ASL, both in reviews in leading forums,[2,95,96] and even in reviews focusing on metabolism.[97,98] The vast majority of researchers and clinicians are thus probably not aware of these strong ALS-DB links and of insulin impairment in ALS.

Why insulin impairment is not detected

We saw that explicit testing of insulin function in ALS points to an impairment. However, if this is the case, ALS patients should have been routinely diagnosed with late DB, which is not the case. How can this be explained?

Here I present a novel answer to this question: **ALS involves excessive insulin-independent glucose uptake (IIGU)**, which in most patients masks their insulin problem. Since DB2 is normally discovered when blood glucose levels are abnormally high, when glucose levels seem normal, deeper tests of insulin function (e.g., OGTT) are usually not done.

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Insulin induces glucose uptake mainly by stimulating the translocation of the Glut4 glucose transporter to the plasma membrane.[99] However, Glut4 translocation is also stimulated independently of insulin, including by AMPK,[100] (nor)epinephrine,[101,102] and calcium.[103,104] Contraction-induced glucose uptake is a major and well-known skeletal muscle mechanism,[103] and so is glucose-induced uptake ('glucose effectiveness').[105] Even calcium concentrations that are below the contraction threshold trigger glucose uptake.[106] Note that Glut4 expression is not limited to skeletal muscle but occurs in brain motor areas as well, including in MTNs.[107,108]

Insulin-independent glucose uptake can be excessive in ALS due to several causes. As noted above, calcium overload is one of the major phenomena of ALS. AMPK is activated by ATP deficiency, which can in turn be induced by two of the major ALS phenomena, mitochondria dysfunction (since mitochondria normally produce most of the cell's ATP) and calcium overload (since the plasma membrane and ER calcium pumps consume ATP[109]). A complete theory of ALS that explains why IIGU occurs is presented in a companion paper.

There is very strong evidence supporting this masked IIGU account. Hypermetabolism identified via FDG-PET clearly occurs in skeletal muscle and low brain motor areas in ALS.[110–115] When added to the widespread evidence for increased resting energy expenditure in ALS detected via indirect calorimetry (including in early-stage patients),[116–123] hypermetabolism is one of the major documented ALS phenomena. While indirect calorimetry does not point to a specific mechanism, FDG-PET directly points to excessive transporter-mediated glucose uptake. ALS patients also show cortical hypometabolism that correlates with gray matter atrophy,[124–126] which may point to glucose deficiency due to excessive glucose uptake by the motor system. Frontal hypometabolism is also a core feature of FTD.[127–131]

At least some of this excessive glucose uptake in ALS is insulin-independent, as shown by increased activated AMPK in patient MTNs,[132,133] early increased sympathetic activity,[134–138] and chronic intracellular MTN calcium.[34,139] The increased sympathetic activity in skeletal muscle is not correlated with ALS disability, duration, or prognosis, showing that it is a core characteristic of the disease.[140,141] In the large subset of patients with impaired insulin function, most of the excessive Glut4-mediated uptake would be insulin-independent.

The existence of a chronic energy consuming process in ALS is also supported by the fact that patients exhibit severe weight loss that is not fully accounted for by reduced food intake.[142–144]

Readers might still wonder why such a gross dysregulation in glucose homeostasis is so commonly not detected. The answer has two parts here. Regarding hyperglycemia, IIGU is normally responsible for more than half of skeletal muscle glucose uptake,[101] so excessive IIGU can mask partially or even fully impaired insulin. Regarding hypoglycemia, there are specific mechanisms to protect from it, counter-regulatory responses (CRRs). Our account implies that as long as insulin is partially functional, CRRs should be moderately hyperactivated. Indeed, all of the CRR components (sympathetic activation (cited above), growth hormone, glucagon, cortisol) are mildly increased in ALS.[65,145–149] Thus, the combination of excessive IIGU and CRRs makes glucose levels seem at around the normal range.

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Why insulin is impaired in ALS

The papers cited earlier reporting insulin impairment in ALS have raised various possible explanations for their results, including reduced glucose uptake by wasted skeletal muscle, physical inactivity inducing IR, stress opposition of insulin signaling via cortisol and (nor)epinephrine, and malnutrition ('starvation diabetes'). However, it has also been acknowledged that these explanations cannot account for the overall pattern of results, which include reduced insulin secretion and receptor expression.

Moreover, these accounts do not address the relationship between ALS and DB1, and the strong association of low pre-onset BMI with increased risk. Since this datum applies for patients many years pre-onset, it is not due to post-onset muscle wasting, inactivity, stress or mulnutrition. In addition, ALS patients do not show hidden pre-onset muscle wasting or inactivity but rather the opposite, since ALS is associated with higher pre-onset physical capacity.[77,84,150,151]

Here I propose a novel answer to this question: **the core pathological processes that damage MTNs in ALS can also damage insulin secretion and/or signaling**, directly or indirectly. As noted above, intracellular calcium toxicity is known to be a major underlying process in ALS. It is clearly possible that the impaired calcium-related proteins are expressed in beta cells, such that the harmful underlying processes occur also in beta cells[1]. Calcium is fundamental to beta cell function, where its acute entry via voltage-gated calcium channels triggers insulin secretion.[99] Hence, calcium toxicity can directly impair beta cells. In addition, chronic calcium can yield chronic insulin secertion, leading to hyperinsulinemia and IR that eventually damage beta cells.

Insulin protection in ALS

Insulin should be protective in ALS. Insulin promotes glucose uptake and protein synthesis.[99] As part of these role, it streamlines cellular energy production and health in a variety of ways. It opposes oxidative stress by promoting GSH synthesis,[152,153] opposes with GSH the apoptosis-promoting effects of H2O2,[154] acts as an anti-inflammatory agent in the immune system,[155] promotes mitochondria health, oxidative phosphorylation, ATP production, and protein synthesis,[156,157] promotes synaptic plasticity,[158] and opposes calcium overload and toxicity.[159–166] Insulin promotes the production of N-Acetylglucosamine (GlcNAc),[167] whose use in O-GlcNAcylation decreases intracellular Ca^{2+} load,[168] H2O2 production, and permeability pore opening.[169] The insulin-induced GSH inhibits stress-induced formation of stress granules,[170] which are strongly associated with TDP-43 accumulation.[33] Conversely, chronic intracellular calcium[171,172] and mitochondria impairment[173,174] induce insulin resistance. Beta cell stress and IR are associated with unfolded proteins,[175–180] permeability pore opening,[181] and calcium toxicity.[171,172,179,182–184] In other words, insulin is an essential component of the stress compensatory mode, and its impairment may lead to decompensation.

[1] A theory of ALS presented in a companion paper points to a specific calcium channel protein as the core cause of ALS, and this protein is indeed expressed in beta cells.

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In summary, **insulin opposes all of the detrimental phenomena that clearly occur in ALS, and these in turn impair insulin signaling**.

Insulin-based DB drugs are indeed protective in ALS. No clinical trials have been done using insulin therapy for ALS. However, several large studies (including all Medicare and a large Swedish population) have found that usage of DB drugs is specifically associated with decreased risk of developing ALS.[185–187] In an all-Taiwan study, moderate insulin use for DB was associated with decreased risk specifically for patients taking non-oral DB drugs.[87]

A single clinical trial for ALS using a DB drug, pioglitazone, has been conducted (as an add-on to riluzole).[188] No benefit has been shown, and the treatment may have even accelerated progression. Pioglitazone does not act directly on the insulin path. It reduces blood glucose levels (thereby sensitizing insulin) mainly by reducing glucose production by the liver, not via direct improvement of insulin signaling. Reducing liver glucose production is not a good strategy in ALS, because ALS cells need glucose for protein synthesis and for opposing oxidative stress, as explained above. Pioglitazone is known to be ineffective and possibly harmful in DB1, and what is harmful for DB1 is also harmful for ALS (see below).

Why DB2 is associated with decreased risk. DB2 involves reduced insulin function, so it could be expected to increase ALS risk. However, it is associated with reduced risk (see references above). There are three possible explanations to this apparent paradox.

First, DB2 is diagnosed when blood glucose is elevated. This normally indicates that insulin function is impaired, but it also indicates that insulin-independent glucose uptake, which is directly induced by the underlying disease processes, is not that excessive. In this account, DB2 is not protective per se, but reflects a reduced effect or risk of the core cause of ALS.

Second, the main pathophysiology in DB2 is IR. IR involves higher blood insulin, which, although promoting further IR, can also induce some insulin signaling, especially in initial or mild DB2. Although weak, this insulin signaling should be protective in ALS.

Finally, many DB2 patients are treated with insulin-based drugs (GLP-1 agonists or insulin itself), which should again oppose the core ALS mechanisms[2]. Here, it is DB2 treatment that opposes the development of ALS. Evidence supporting this account was cited above.

In the second and third accounts, insulin is directly protective in ALS.

Insulin trajectories, DB1, and BMI in ALS

Insulin function normally decreases with aging,[190,191] but in ALS, several trajectories are possible. The main factors that distinguish between the different scenarios is whether and when beta cell impairment and insulin hypersecretion occur. Here I discuss the possible lifetime trajectories of insulin in ALS and their effect on patient metabolism, body mass index (BMI), symptoms, and the association with DB1. This includes an account of why higher pre-onset BMI can be associated with both decreased and increased ALS risk.

A brief summary of insulin's relationship with BMI is in order. Acute insulin promotes glucose uptake by the motor system, and quick insulin clearance from blood allows lipolysis and

[2]See below why this argument is less valid for DB1.

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reduces lipogenesis. Conversely, chronic lower-grade insulin yields chronic insulin signaling, which channels more glucose towards visceral adipose tissue, opposes lipolysis, and promotes lipogenesis and higher BMI.[189] Severely impaired insulin secretion, or severe desensitization of insulin signaling by its prolonged hypersecretion, stronly impair lipogenesis and promote fat-based metabolism (which induces lipolysis) to compensate for cellular glucose deficiency. This results in lower BMI.

Normal secretion with late impairment. In the first scenario, insulin secretion capacity is not affected by the disease until it is normally reduced with aging. Since both insulin and IIGU promote glucose uptake, and since ALS involves excessive IIGU, overall pre-onset glucose uptake in this scenario should be higher, and glucose levels should be on the lower side. Indeed, in a large study in Sweden, ALS was associated with lower blood glucose from 20 years pre-onset to onset.[192]

In this scenario, skeletal muscle and other cells uptake and utilize more glucose than they normally do, so less glucose is available for muscle and adipose tissue storage. Moreover, decreased blood glucose levels imply reduced insulin secretion even though secretion capacity is intact (as assumed in this scenario). Reduced secretion diminishes energy storage and stimulates fat-based energy production and lipolysis. As a result, the person is expected to be leaner than the average. Indeed, in both country-wide and single clinic studies, low pre-onset BMI was found to be strongly associated with increased ALS risk.[77–85]

Here, the aging-related reduction in insulin (and possibly in other protective agents, e.g., steroids) is a trigger for the appearance of disease symptoms. Higher BMI is associated with decreased risk in these studies and with longer survival in a meta-analysis[193] because it indicates weaker core disease processes (as in the DB2 account), and because it is contrasted with low BMI, which is a characteristic of the present scenario.

Increased secretion with late impairment. In a second scenario, insulin secretion is chronically higher than normal most life. This can be ALS-independent, or driven by ALS processes (e.g., chronically high beta cell calcium). As explained above, this scenario eventually leads to both IR and impaired secretion, each of which can trigger the disease symptoms.

Unlike in the previous scenario, the chronically increased insulin secretion in the present one can induce higher pre-onset BMI and visceral fat. This accords with the Swabia cohort in which ALS was associated with high BMI 20 to 70 years pre-onset.[194] Moreover, a recent Michigan cohort was reported to show BMI gain 10-15 years pre-onset, followed by BMI loss 5 years pre-onset.[195] This is precisely the pattern predicted here: the initial BMI gain is due to chronic secretion possibly followed by mild IR, while the subsequent BMI loss is due to the collapse of insulin function and the core disease processes.

Body composition studies provide abundant evidence for this scenario in ALS. Reported results include increased visceral as opposed to subcutaneous fat at onset, even when total body fat is similar to controls,[196] higher fat mass with lower fat-free mass,[118] loss of lean mass and BMI and gain of fat mass with disease progression,[197,198] and a lower/higher percentage of muscle/fat mass, respectively.[199]

In this scenario, insulin impairment again seems to be the specific event that triggers the appearance of ALS symptoms.

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In a third scenario, insulin secretion is increased as in the second scenario, but ALS symptoms appear before IR does. This is possible when the core problem or IR affect MTNs faster than they affect beta cells.

Early impairment (early DB, DB1). In a fourth scenario, insulin secretion is reduced at an early age, due to ALS processes or independently. In this case, the protection that insulin provides is not present, resulting in increased ALS risk. This explains increased ALS risk with early DB (cited above), which is usually insulin-dependent (DB1).

DB1 patients normally receive insulin treatment, which should delay ALS onset or maybe even prevent it altogether. There are two reasons why insulin does not always prevent the disease. First, it is notoriously difficult to balance insulin treatment, so patients commonly undergo episodes of low insulin levels, during which their cells are exposed to damage. This might be why in the all-Taiwan study cited above of ALS in DB,[87] high insulin use, indicating a prolonged severe damage to insulin function, showed a non-significant association with increased risk.

Second, insulin treatment is calibrated by glucose levels, but due to the excessive IIGU in ALS, seemingly normal glucose levels do not indicate that a sufficient amount of glucose is used by the insulin path (which is essential for protein synthesis, opposing oxidative stress, etc.). In other words, these comorbid patients probably do not receive enough insulin, and their insulin treatment only brings them to a state similar to that of the first scenario.

No impairment. Finally, it is still possible for insulin secretion and signaling to be intact throughout life, including during disease appearance and initial progression. In this scenario, the disease is completely driven by its core causes and aging. For example, steroids also decline with aging, and are generally protective by reversing the aging-related increase in brain calcium currents.[200] However, since chronic intracellular calcium induces IR,[171,172,179,201,202] this scenario is less likely than the other ones.

In summary, there are several possible patterns of insulin secretion, IR, glucose levels, and BMI in ALS. **In the more likely scenarios, the impairment of insulin function is a direct trigger of disease symptoms**. The severe weight loss shown in ALS is caused not only by dysphagia and energy-consuming core processes (see above), but also by strongly impaired insulin. This explains the association of low BMI and DB1 with increased risk, and that of high BMI with decreased risk. However, in a common scenario, impaired signaling can be preceded by chronically higher secretion, explaining why higher BMI can be associated also with increased risk.

Tests and Treatment

Therapy. There are several lines of ALS treatment implied by the analysis here, the main one being insulin-based DB drugs. Since insulin opposes the main ALS processes and its impairment is directly associated with the appearance of symptoms, insulin-based drugs might slow down disease progression. In MTNs whose axons have only started degenerating, treatment may even reverse the process.

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The specific insulin-based treatment to be used depends on beta cell insulin secretion capacity. In cases where endogenous insulin secretion is possible (as in most DB2 patients), GLP-1 agonists are currently preferred over insulin, due to reduced risk of hypoglycemia.[203] However, if beta cells are already damaged to the extent that endogenous insulin secretion in meaningful amounts is not possible, exogenous insulin should be used.

To reduce hypoglycemia risk, therapy can be combined with a hypercaloric carb diet (HCD). Such a diet should have additional benefits in ALS, since additional glucose would relieve cellular stress, promote protein folding, and provide raw material for lipogenesis, countering the tissue wasting shown in ALS. Indeed, HCD (without insulin) showed better results than a control diet in a small ALS clinical trial.[204]

Tests. Using insulin-based therapy for all ALS patients would require clinical trials and an approval process. However, such a therapy is already justified in patients with demonstrated insulin dysfunction. As part of ALS diagnosis, patients should undergo DB classification tests focusing on insulin function.

The simplest test is the oral glucose tolerance test, but there are several additional options (intravenous glucose, insulin or glucagon tolerance tests, with or without clamps). A highly informative test is a glucose clamp with somatostatin infusions to suppress endogenous insulin secretion.[105] This test isolates the insulin-independent component of glucose uptake, and can directly alert that it is excessive. Thus, it might be capable of identifying many of the cases where insulin secretion and insulin-stimulated glucose uptake are low but are still within the 'normal' range, along with seemingly normal glucose levels.

In many patients, the test results would show insulin impairment at levels standardly defined as DB or pre-DB, justifying DB therapy. In these cases, insulin-based rather than other DB drugs should be preferably used, because they are expected to have a greater benefit in ALS (see pioglitazone discussion above). Metformin reduces hepatic glucose production and thus alleviates IR, but it also activates AMPK,[205] which might stimulate the excessive glucose uptake shown in ALS [3].

It is not clear whether patients showing increased insulin secretion at diagnosis (the third scenario above, where symptoms appear before insulin diminishes) should be treated with insulin. On one hand, they already have too much basal insulin. On the other hand, their current insulin levels have not managed to protect their MTNs (symptoms have already appeared), and exogenous insulin may both protect their MTNs and relieve the pressure off their beta cells.

It is reassuring that a systematic review has found no evidence of DB drugs being associated with higher ALS risk.[207]

Other treatment. Insulin-based therapy can be combined with other drugs. Calcium channel blockers, which reduce calcium load, are associated with reduced ALS risk.[186,187] Clinical trials using nimodipine alone did not help in ALS,[208,209] but daily oral use of verapamil, with insulin treatment, improved beta cell function in adult recent onset DB1 in a human phase II clinical trial.[210] Anti-oxidative stress agents such as the drugs currently approved for ALS might also help, but it is not clear that using them would be cost-effective.

[3] Metformin was also harmful to females in the SOD1 mouse ALS model.[206]

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Discussion

In this paper I analyzed the existing ALS literature to conclude that

- Insulin opposes all of the salient pathophysiological phenomena identified in ALS, and these in turn oppose insulin signaling.
- Insulin secretion and/or signaling have been found to be impaired in non-DB ALS in almost all of the studies that have explicitly tested for them.
- Insulin impairment is usually not diagnosed, most likely because it is masked by excessive insulin-independent glucose uptake.
- Different insulin impairment trajectories can explain why early/late DB are associated with increased/decreased risk of ALS, respectively, and the BMI data in ALS.
- DB drugs including insulin-based therapy have been found to be protective in ALS in several large retrospective studies.

The analysis is supported by very strong existing evidence that is not recognized by most of the research and medical communities. This paper is the first to point to the wide extent of the problem, and provides novels accounts of the seeming paradoxical glucose and DB phenomena.

Insulin impairment is not the core cause of ALS, which is most likely calcium overload. However, insulin impairment strongly facilitates ALS and is a major trigger of ALS symptoms. Insulin-based therapy would not be able to reverse MTN death or total axonal degeneration, but it has a good chance of considerably slowing disease progression if started early enough.

Almost anybody who has ever examined insulin signaling in ALS has found that it is impaired at the group level. DB2, which involves higher blood insulin and in many cases insulin-based drugs, is associated with reduced risk. DB drugs have been independently found to be associated with reduced risk. These three data points alone, even without the new theoretical analysis presented here, justify DB screening tests in ALS patients, followed by DB treatment if positive.

All of the professional infrastructure for insulin-based therapy in ALS is already in place. The OGTT and other related tests are standard tests routinely administered in medical centers. If test results show that the patient has DB according to standard norms, treatment using DB drugs is fully justified. Treating patients for DB does not require new clinical trials, even if the analysis here shows that the treatment actually targets their ALS. The only non-standard recommendation made here is that treatment would not start with metformin or other non-insulin-based drugs (or life-style changes), but immediately with insulin-based therapy.

Whether insulin manages to help or not is an empirical question. ALS is diagnosed when the NMJ has accumulated enough damage to interfere with muscle function. It is possible that at this point, exogenous insulin cannot slow down the negative chronic processes within MTNs, which include mutually enforcing calcium toxicity, oxidative stress, inflammation, and the apoptosis arms of cellular stress responses. If it helps, it would probably help only patients who were diagnosed early enough.

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Most of the evidence brought here is from sALS[4]. Although the etiologies of sALS and fALS are probably different, they show a converging pathophysiology. Thus, our conclusions may be applicable to fALS as well. This should be corroborated in future research.

The analysis here applies to FTD patients showing ALS symptoms, so at least to behavioral variant FTD. Unlike in ALS, the link between dementia and IR is well-known,[211,212] to the extent that some forms of dementia are thought to be 'type-3 diabetes'.[213] FTD patients were specifically shown to have DB much more than controls.[214] Thus, insulin-based therapy is a natural direction in FTD.

The scenario in which insulin secretion is impaired early (the fourth one) explains comorbidity with DB1. It also raises the interesting possibility that at least some cases of DB1 have the same underlying cause as ALS, but do not show ALS symptoms because their insulin treatment is successful.

A companion paper presents a complete theory of ALS according to which ALS is an autoimmune disease that targets calcium channels. That paper also points to the precise protein whose impairment causes the disease. The presentation here only assumes that calcium toxicity is a major phenomenon in ALS (which is consensual) and is otherwise independent of that theory.

I hope that this paper will contribute to reducing the suffering of ALS patients and their families and caretakers.

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Conflicts of interest

The author declares no conflicts of interest.

References

[1] Leigh N, Sreedharan J, Wijesekera L. Motor neuron disease: Amyotrophic lateral sclerosis. In: Neuroscience in the 21st Century: From Basic to Clinical, Second Edition. Springer New York; 2016. p. 3799–3841.

[2] Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nature Reviews Disease Primers. 2017;3(1):1–19.

[4] Although it is possible that the early OGTT results had included some fALS patients.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[3] Woollacott IO, Rohrer JD. The clinical spectrum of sporadic and familial forms of frontotemporal dementia. Journal of neurochemistry. 2016;138:6–31.

[4] Arrant A, Roberson E. Frontotemporal Dementia. In: The Cerebral Cortex in Neurodegenerative and Neuropsychiatric Disorders. Elsevier; 2017. p. 141–175.

[5] Turnbull J. Is edaravone harmful? (A placebo is not a control). Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018;19(7-8):477–482.

[6] Jaiswal MK. Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. Medicinal Research Reviews. 2019;39(2):733–748.

[7] Paganoni S, Hendrix S, Dickson SP, Knowlton N, Macklin EA, Berry JD, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. Muscle & nerve. 2021;63(1):31–39.

[8] Ito Y, Yamada M, Tanaka H, Aida K, Tsuruma K, Shimazawa M, et al. Involvement of CHOP, an ER-stress apoptotic mediator, in both human sporadic ALS and ALS model mice. Neurobiology of disease. 2009;36(3):470–476.

[9] Ilieva EV, Ayala V, Jové M, Dalfó E, Cacabelos D, Povedano M, et al. Oxidative and endoplasmic reticulum stress interplay in sporadic amyotrophic lateral sclerosis. Brain. 2007;130(12):3111–3123.

[10] Balendra R, Isaacs AM. C9orf72-mediated ALS and FTD: multiple pathways to disease. Nat Revs Neurol. 2018;14(9):544–558.

[11] Hall CE, Yao Z, Choi M, Tyzack GE, Serio A, Luisier R, et al. Progressive motor neuron pathology and the role of astrocytes in a human stem cell model of VCP-related ALS. Cell reports. 2017;19(9):1739–1749.

[12] Prause J, Goswami A, Katona I, Roos A, Schnizler M, Bushuven E, et al. Altered localization, abnormal modification and loss of function of Sigma receptor-1 in amyotrophic lateral sclerosis. Human molecular genetics. 2013;22(8):1581–1600.

[13] Woehlbier U, Colombo A, Saaranen MJ, Pérez V, Ojeda J, Bustos FJ, et al. ALS-linked protein disulfide isomerase variants cause motor dysfunction. The EMBO journal. 2016;35(8):845–865.

[14] Yang Q, Guo Zb. Polymorphisms in protein disulfide isomerase are associated with sporadic amyotrophic lateral sclerosis in the Chinese Han population. International Journal of Neuroscience. 2016;126(7):607–611.

[15] Kwok CT, Morris AG, Frampton J, Smith B, Shaw CE, de Belleroche J. Association studies indicate that protein disulfide isomerase is a risk factor in amyotrophic lateral sclerosis. Free Radical Biology and Medicine. 2013;58:81–86.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[16] Gonzalez-Perez P, Woehlbier U, Chian RJ, Sapp P, Rouleau GA, Leblond CS, et al. Identification of rare protein disulfide isomerase gene variants in amyotrophic lateral sclerosis patients. Gene. 2015;566(2):158–165.

[17] Sasaki S. Endoplasmic reticulum stress in motor neurons of the spinal cord in sporadic amyotrophic lateral sclerosis. Journal of Neuropathology & Experimental Neurology. 2010;69(4):346–355.

[18] Dodge JC, Treleaven CM, Fidler JA, Tamsett TJ, Bao C, Searles M, et al. Metabolic signatures of amyotrophic lateral sclerosis reveal insights into disease pathogenesis. Proceedings of the National Academy of Sciences. 2013;110(26):10812–10817.

[19] Nardo G, Pozzi S, Pignataro M, Lauranzano E, Spano G, Garbelli S, et al. Amyotrophic lateral sclerosis multiprotein biomarkers in peripheral blood mononuclear cells. PloS one. 2011;6(10):e25545.

[20] Sarlette A, Krampfl K, Grothe C, Neuhoff Nv, Dengler R, Petri S. Nuclear erythroid 2-related factor 2-antioxidative response element signaling pathway in motor cortex and spinal cord in amyotrophic lateral sclerosis. Journal of Neuropathology & Experimental Neurology. 2008;67(11):1055–1062.

[21] Ikawa M, Okazawa H, Tsujikawa T, Matsunaga A, Yamamura O, Mori T, et al. Increased oxidative stress is related to disease severity in the ALS motor cortex: a PET study. Neurology. 2015;84(20):2033–2039.

[22] Blasco H, Garcon G, Patin F, Veyrat-Durebex C, Boyer J, Devos D, et al. Panel of oxidative stress and inflammatory biomarkers in ALS: a pilot study. Canadian Journal of Neurological Sciences. 2017;44(1):90–95.

[23] Weiduschat N, Mao X, Hupf J, Armstrong N, Kang G, Lange D, et al. Motor cortex glutathione deficit in ALS measured in vivo with the J-editing technique. Neuroscience letters. 2014;570:102–107.

[24] Ferrante RJ, Browne SE, Shinobu LA, Bowling AC, Baik MJ, MacGarvey U, et al. Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. Journal of neurochemistry. 1997;69(5):2064–2074.

[25] Smith RG, Henry YK, Mattson MP, Appel SH. Presence of 4-hydroxynonenal in cerebrospinal fluid of patients with sporadic amyotrophic lateral sclerosis. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1998;44(4):696–699.

[26] Pedersen WA, Fu W, Keller JN, Markesbery WR, Appel S, Smith RG, et al. Protein modification by the lipid peroxidation product 4-hydroxynonenal in the spinal cords of amyotrophic lateral sclerosis patients. Annals of neurology. 1998;44(5):819–824.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[27] Mitsumoto H, Santella RM, Liu X, Bogdanov M, Zipprich J, Wu HC, et al. Oxidative stress biomarkers in sporadic ALS. Amyotrophic Lateral Sclerosis. 2008;9(3):177–183.

[28] Blasco H, Veyrat-Durebex C, Bocca C, Patin F, Vourc'h P, Kouassi Nzoughet J, et al. Lipidomics reveals cerebrospinal-fluid signatures of ALS. Scientific reports. 2017;7(1):1–10.

[29] Simpson E, Henry Y, Henkel J, Smith R, Appel SH. Increased lipid peroxidation in sera of ALS patients: a potential biomarker of disease burden. Neurology. 2004;62(10):1758–1765.

[30] Shaw PJ, Ince PG, Falkous G, Mantle D. Oxidative damage to protein in sporadic motor neuron disease spinal cord. Annals Neurol. 1995;38(4):691–695.

[31] Béland LC, Markovinovic A, Jakovac H, De Marchi F, Bilic E, Mazzini L, et al. Immunity in amyotrophic lateral sclerosis: Blurred lines between excessive inflammation and inefficient immune responses. Brain Communications. 2020;2(2):fcaa124.

[32] Beers DR, Appel SH. Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. The Lancet Neurology. 2019;18(2):211–220.

[33] Prasad A, Bharathi V, Sivalingam V, Girdhar A, Patel BK. Molecular mechanisms of TDP-43 misfolding and pathology in amyotrophic lateral sclerosis. Frontiers in molecular neuroscience. 2019;12:25.

[34] Siklós L, Engelhardt J, Harati Y, Smith RG, Joó F, Appel SH. Ultrastructural evidence for altered calcium in motor nerve terminals in amyotrophc lateral sclerosis. Annals of neurology. 1996;39(2):203–216.

[35] Appel SH, Beers D, Siklos L, Engelhardt JI, Mosier DR. Calcium: the darth vader of ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2001;2(1):47–54.

[36] Patai R, Nógrádi B, Engelhardt JI, Siklós L. Calcium in the pathomechanism of amyotrophic lateral sclerosis–Taking center stage? Biochemical and biophysical research communications. 2017;483(4):1031–1039.

[37] Van Den Bosch L. Amyotrophic lateral sclerosis: mechanisms and therapeutic strategies. In: Disease-Modifying Targets in Neurodegenerative Disorders. Elsevier; 2017. p. 277–296.

[38] Larrodé P, Calvo AC, Moreno-Martínez L, de la Torre M, Moreno-García L, Molina N, et al. DREAM-dependent activation of astrocytes in amyotrophic lateral sclerosis. Molecular Neurobiology. 2018;55(1):1–12.

[39] Patel AN, Mathew D. A study of gene expression changes in human spinal and oculomotor neurons; identifying potential links to sporadic ALS. Genes. 2020;11(4):448.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[40] King AE, Woodhouse A, Kirkcaldie MT, Vickers JC. Excitotoxicity in ALS: Overstimulation, or overreaction? Experimental neurology. 2016;275:162–171.

[41] Wiedemann FR, Manfredi G, Mawrin C, Beal MF, Schon EA. Mitochondrial DNA and respiratory chain function in spinal cords of ALS patients. Journal of neurochemistry. 2002;80(4):616–625.

[42] Raman R, Allen SP, Goodall EF, Kramer S, Ponger LL, Heath PR, et al. Gene expression signatures in motor neurone disease fibroblasts reveal dysregulation of metabolism, hypoxia-response and RNA processing functions. Neuropathology and applied neurobiology. 2015;41(2):201–226.

[43] Singh T, Jiao Y, Ferrando LM, Yablonska S, Li F, Horoszko EC, et al. Neuronal mitochondrial dysfunction in sporadic amyotrophic lateral sclerosis is developmentally regulated. Scientific reports. 2021;11(1):1–16.

[44] Hor JH, Santosa MM, Lim VJW, Ho BX, Taylor A, Khong ZJ, et al. ALS motor neurons exhibit hallmark metabolic defects that are rescued by SIRT3 activation. Cell Death & Differentiation. 2021;28(4):1379–1397.

[45] Yamashita T, Hatakeyama T, Sato K, Fukui Y, Hishikawa N, Takemoto M, et al. Hypoxic stress visualized in the cervical spinal cord of ALS patients. Neurological Research. 2021;43(6):429–433.

[46] Yu CH, Davidson S, Harapas CR, Hilton JB, Mlodzianoski MJ, Laohamonthonkul P, et al. TDP-43 triggers mitochondrial DNA release via mPTP to activate cGAS/STING in ALS. Cell. 2020;183(3):636–649.

[47] Wobst HJ, Mack KL, Brown DG, Brandon NJ, Shorter J. The clinical trial landscape in amyotrophic lateral sclerosisPast, present, and future. Medicinal research reviews. 2020;40(4):1352–1384.

[48] Steinke J, Tyler HR. The association of amyotrophic lateral sclerosis (motor neuron disease) and carbohydrate intolerance, a clinical study. Metabolism. 1964;13(11):1376–1381.

[49] Gotoh F, Kitamura A, Koto A, Kataoka K, Atsuji H. Abnormal insulin secretion in amyotrophic lateral sclerosis. Journal of the neurological sciences. 1972;16(2):201–207.

[50] Saffer D, Morley J, Bill P. Carbohydrate metabolism in motor neurone disease. Journal of Neurology, Neurosurgery & Psychiatry. 1977;40(6):533–537.

[51] Shimizu T, Honda M, Ohashi T, Tsujino M, Nagaoka U, Kawata A, et al. Hyperosmolar hyperglycemic state in advanced amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2011;12(5):379–381.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[52] Ngo S, Steyn F, Huang L, Mantovani S, Pfluger C, Woodruff T, et al. Altered expression of metabolic proteins and adipokines in patients with amyotrophic lateral sclerosis. Journal of the neurological sciences. 2015;357(1-2):22–27.

[53] Araki K, Araki A, Honda D, Izumoto T, Hashizume A, Hijikata Y, et al. TDP-43 regulates early-phase insulin secretion via CaV1.2-mediated exocytosis in islets. The Journal of clinical investigation. 2019;129(9):3578–3593.

[54] Collis W, Engel W. Glucose metabolism in five neuromuscular disorders. Neurology. 1968;18(9):915–915.

[55] Ionaşescu V, Luca N. Studies on carbohydrate metabolism in amyotrophic lateral sclerosis and hereditary proximal spinal muscular atrophy. Acta Neurologica Scandinavica. 1964;40(1):47–57.

[56] Utterback RA, Cummins AJ, Cape CA, Goldenberg J. Pancreatic function in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 1970;33(4):544–547.

[57] Shahani B, Davies-Jones G, Russell WR. Motor neurone disease: Further evidence for an abnormality of nerve metabolism. Journal of Neurology, Neurosurgery & Psychiatry. 1971;34(2):185–191.

[58] Moore W, Festoff B. INSULIN-RECEPTORS (IR) AND INSULIN SENSITIVITY (IS) IN AMYOTROPHIC LATERAL SCLEROSIS (ALS). In: Neurology. vol. 32. LIPPINCOTT-RAVEN PUBL 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106; 1982. p. A105–A105.

[59] Moxley RT, Griggs RC, Forbes GB, Goldblatt D, Donohoe K. Influence of muscle wasting on oral glucose tolerance testing. Clinical Science. 1983;64(6):601–609.

[60] Murai A, MIYAHARA T, TANAKA T, KANEKO T, SAKO Y, KAMEYAMA M. Abnormalities of lipoprotein and carbohydrate metabolism in degenerative diseases of the nervous system-motor neuron disease and spinocerebellar degeneration. The Tohoku Journal of Experimental Medicine. 1983;139(4):365–376.

[61] Reyes ET, Perurena OH, Festoff BW, Jorgensen R, Moore WV. Insulin resistance in amyotrophic lateral sclerosis. Journal of the neurological sciences. 1984;63(3):317–324.

[62] Harno K, Rissanen A, Palo J. Glucose tolerance in amyotrophic lateral sclerosis. Acta neurologica scandinavica. 1984;70(6):451–455.

[63] Pradat PF, Bruneteau G, Gordon PH, Dupuis L, Bonnefont-Rousselot D, Simon D, et al. Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2010;11(1-2):166–171.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[64] Nygren I, Fagius J. High resting level and weak response of baroreflex-governed sympathetic outflow in amyotrophic lateral sclerosis. Muscle & nerve. 2011;43(3):432–440.

[65] Li JY, Cui LY, Sun XH, Shen Dc, Yang XZ, Liu Q, et al. Alterations in metabolic biomarkers and their potential role in amyotrophic lateral sclerosis. Annals of Clinical and Translational Neurology. 2022;9(7):1027–1038.

[66] Harris MD, Davidson MB, Rosenberg CS. Insulin antagonism is not a primary abnormality of amyotrophic lateral sclerois but is related to disease severity. The Journal of Clinical Endocrinology & Metabolism. 1986;63(1):41–46.

[67] Astin K, Wilde C, Davies-Jones G. Glucose metabolism and insulin response in the plasma and CSF in motor neurone disease. Journal of the neurological Sciences. 1975;25(2):205–210.

[68] Cumings J. Biochemical aspects. Proceedings of the Royal Society of Medicine. 1962;55:1023–1024.

[69] Wuolikainen A, Jonsson P, Ahnlund M, Antti H, Marklund SL, Moritz T, et al. Multi-platform mass spectrometry analysis of the CSF and plasma metabolomes of rigorously matched amyotrophic lateral sclerosis, Parkinson's disease and control subjects. Molecular BioSystems. 2016;12(4):1287–1298.

[70] Ahmed RM, MacMillan M, Bartley L, Halliday GM, Kiernan MC, Hodges JR, et al. Systemic metabolism in frontotemporal dementia. Neurology. 2014;83(20):1812–1818.

[71] Turner MR, Goldacre R, Ramagopalan S, Talbot K, Goldacre MJ. Autoimmune disease preceding amyotrophic lateral sclerosis: an epidemiologic study. Neurology. 2013;81(14):1222–1225.

[72] Mariosa D, Kamel F, Bellocco R, Ye W, Fang F. Association between diabetes and amyotrophic lateral sclerosis in Sweden. European journal of neurology. 2015;22(11):1436–1442.

[73] Sun Y, Lu CJ, Chen RC, Hou WH, Li CY. Risk of amyotrophic lateral sclerosis in patients with diabetes: a nationwide population-based cohort study. Journal of Epidemiology. 2015;p. JE20140176.

[74] Kioumourtzoglou MA, Rotem RS, Seals RM, Gredal O, Hansen J, Weisskopf MG. Diabetes mellitus, obesity, and diagnosis of amyotrophic lateral sclerosis: a population-based study. JAMA neurology. 2015;72(8):905–911.

[75] Ferri L, Ajdinaj P, Rispoli MG, Carrarini C, Barbone F, D'Ardes D, et al. Diabetes mellitus and amyotrophic lateral sclerosis: a systematic review. Biomolecules. 2021;11(6):867.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[76] Wei QQ, Chen Y, Cao B, Ou RW, Zhang L, Hou Y, et al. Blood hemoglobin A1c levels and amyotrophic lateral sclerosis survival. Molecular neurodegeneration. 2017;12(1):1–7.

[77] Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. Neurology. 2002;59(5):773–775.

[78] O'Reilly ÉJ, Wang H, Weisskopf MG, Fitzgerald KC, Falcone G, McCullough ML, et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013;14(3):205–211.

[79] Gallo V, Wark PA, Jenab M, Pearce N, Brayne C, Vermeulen R, et al. Prediagnostic body fat and risk of death from amyotrophic lateral sclerosis: the EPIC cohort. Neurology. 2013;80(9):829–838.

[80] Huisman MH, Seelen M, van Doormaal PT, de Jong SW, de Vries JH, van der Kooi AJ, et al. Effect of presymptomatic body mass index and consumption of fat and alcohol on amyotrophic lateral sclerosis. JAMA neurology. 2015;72(10):1155–1162.

[81] Mariosa D, Beard JD, Umbach DM, Bellocco R, Keller J, Peters TL, et al. Body mass index and amyotrophic lateral sclerosis: a study of US military veterans. American journal of epidemiology. 2017;185(5):362–371.

[82] Lian L, Liu M, Cui L, Guan Y, Liu T, Cui B, et al. Environmental risk factors and amyotrophic lateral sclerosis (ALS): a case-control study of ALS in China. Journal of Clinical Neuroscience. 2019;66:12–18.

[83] Nakken O, Meyer HE, Stigum H, Holmøy T. High BMI is associated with low ALS risk: a population-based study. Neurology. 2019;93(5):e424–e432.

[84] Diekmann K, Kuzma-Kozakiewicz M, Piotrkiewicz M, Gromicho M, Grosskreutz J, Andersen PM, et al. Impact of comorbidities and co-medication on disease onset and progression in a large German ALS patient group. Journal of Neurology. 2020;267(7):2130–2141.

[85] Schumacher J, Peter R, Nagel G, Rothenbacher D, Rosenbohm A, Ludolph A, et al. Statins, diabetes mellitus and prognosis of amyotrophic lateral sclerosis: data from 501 patients of a population-based registry in southwest Germany. European journal of neurology. 2020;27(8):1405–1414.

[86] D'Ovidio F, d'Errico A, Carnà P, Calvo A, Costa G, Chiò A. The role of pre-morbid diabetes on developing amyotrophic lateral sclerosis. European journal of neurology. 2018;25(1):164–170.

[87] Tsai CP, Lee JKW, Lee CTC. Type II diabetes mellitus and the incidence of amyotrophic lateral sclerosis. Journal of Neurology. 2019;266(9):2233–2243.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[88] Tsai CP, Hu C, Lee CTC. Finding diseases associated with amyotrophic lateral sclerosis: A total population-based case–control study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2019;20(1-2):82–89.

[89] Mitchell CS, Hollinger SK, Goswami SD, Polak MA, Lee RH, Glass JD. Antecedent disease is less prevalent in amyotrophic lateral sclerosis. Neurodegenerative Diseases. 2015;15(2):109–113.

[90] Seelen M, van Doormaal PT, Visser AE, Huisman MH, Roozekrans MH, de Jong SW, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. Journal of neurology. 2014;261(10):1949–1956.

[91] Körner S, Kollewe K, Ilsemann J, Müller-Heine A, Dengler R, Krampfl K, et al. Prevalence and prognostic impact of comorbidities in amyotrophic lateral sclerosis. European journal of neurology. 2013;20(4):647–654.

[92] Jawaid A, Salamone A, Strutt A, Murthy S, Wheaton M, McDowell E, et al. ALS disease onset may occur later in patients with pre-morbid diabetes mellitus. European Journal of Neurology. 2010;17(5):733–739.

[93] Zhang L, Chen L, Fan D. The protective role of pre-morbid type 2 diabetes in patients with amyotrophic lateral sclerosis: a center-based survey in China. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2020;21(3-4):209–215.

[94] Chen L, Xu L, Tang L, Xia K, Tian D, Zhang G, et al. Trends in the clinical features of amyotrophic lateral sclerosis: A 14-year Chinese cohort study. European Journal of Neurology. 2021;28(9):2893–2900.

[95] Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. New England Journal of Medicine. 2017;377(2):162–172.

[96] Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, et al. Amyotrophic lateral sclerosis. The Lancet. 2022;400:1363–1380.

[97] D'Amico E, Grosso G, Nieves JW, Zanghì A, Factor-Litvak P, Mitsumoto H. Metabolic abnormalities, dietary risk factors and nutritional management in amyotrophic lateral sclerosis. Nutrients. 2021;13(7):2273.

[98] Guillot SJ, Bolborea M, Dupuis L. Dysregulation of energy homeostasis in amyotrophic lateral sclerosis. Current Opinion in Neurology. 2021;34(5):773–780.

[99] Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiological reviews. 2018;98(4):2133–2223.

[100] Osler ME, Zierath JR. Minireview: adenosine 5'-monophosphate-activated protein kinase regulation of fatty acid oxidation in skeletal muscle. Endocrinology. 2008;149(3):935–941.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[101] Sato M, Dehvari N, Öberg AI, Dallner OS, Sandström AL, Olsen JM, et al. Improving type 2 diabetes through a distinct adrenergic signaling pathway involving mTORC2 that mediates glucose uptake in skeletal muscle. Diabetes. 2014;63(12):4115–4129.

[102] Shiuchi T, Toda C, Okamoto S, Coutinho EA, Saito K, Miura S, et al. Induction of glucose uptake in skeletal muscle by central leptin is mediated by muscle β2-adrenergic receptor but not by AMPK. Scientific reports. 2017;7(1):1–11.

[103] Jessen N, Goodyear LJ. Contraction signaling to glucose transport in skeletal muscle. Journal of Applied Physiology. 2005;99(1):330–337.

[104] Wright DC, Hucker KA, Holloszy JO, Han DH. Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. Diabetes. 2004;53(2):330–335.

[105] Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN. Role of glucose effectiveness in the determination of glucose tolerance. Diabetes care. 1996;19(9):1018–1030.

[106] Youn J, Gulve E, Holloszy J. Calcium stimulates glucose transport in skeletal muscle by a pathway independent of contraction. American Journal of Physiology-Cell Physiology. 1991;260(3):C555–C561.

[107] El Messari S, Aït-Ikhlef A, Ambroise DH, Penicaud L, Arluison M. Expression of insulin-responsive glucose transporter GLUT4 mRNA in the rat brain and spinal cord: an in situ hybridization study. Journal of chemical neuroanatomy. 2002;24(4):225–242.

[108] Choeiri C, Staines W, Messier C. Immunohistochemical localization and quantification of glucose transporters in the mouse brain. Neuroscience. 2002;111(1):19–34.

[109] Smith IC, Bombardier E, Vigna C, Tupling AR. ATP consumption by sarcoplasmic reticulum Ca2+ pumps accounts for 40-50% of resting metabolic rate in mouse fast and slow twitch skeletal muscle. PloS one. 2013;8(7):e68924.

[110] Cistaro A, Valentini MC, Chiò A, Nobili F, Calvo A, Moglia C, et al. Brain hypermetabolism in amyotrophic lateral sclerosis: a FDG PET study in ALS of spinal and bulbar onset. European journal of nuclear medicine and molecular imaging. 2012;39(2):251–259.

[111] Canosa A, Pagani M, Cistaro A, Montuschi A, Iazzolino B, Fania P, et al. 18F-FDG-PET correlates of cognitive impairment in ALS. Neurology. 2016;86(1):44–49.

[112] Pagani M, Chiò A, Valentini MC, Öberg J, Nobili F, Calvo A, et al. Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis. Neurology. 2014;83(12):1067–1074.

[113] Van Laere K, Vanhee A, Verschueren J, De Coster L, Driesen A, Dupont P, et al. Value of 18fluorodeoxyglucose–positron-emission tomography in amyotrophic lateral sclerosis: a prospective study. JAMA neurology. 2014;71(5):553–561.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[114] Sala A, Iaccarino L, Fania P, Vanoli EG, Fallanca F, Pagnini C, et al. Testing the diagnostic accuracy of [18F] FDG-PET in discriminating spinal-and bulbar-onset amyotrophic lateral sclerosis. European Journal of Nuclear Medicine and Molecular Imaging. 2019;46(5):1117–1131.

[115] Zanovello M, Sorarù G, Campi C, Anglani M, Spimpolo A, Berti S, et al. Brainstem glucose hypermetabolism in ALS/FTD and shorten survival: a 18F-FDG PET/MR study. Journal of Nuclear Medicine. 2021;.

[116] Vaisman N, Lusaus M, Nefussy B, Niv E, Comaneshter D, Hallack R, et al. Do patients with amyotrophic lateral sclerosis (ALS) have increased energy needs? Journal of the neurological sciences. 2009;279(1-2):26–29.

[117] Cattaneo M, Jesus P, Lizio A, Fayemendy P, Guanziroli N, Corradi E, et al. The hypometabolic state: a good predictor of a better prognosis in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2022;93(1):41–47.

[118] Steyn FJ, Ioannides ZA, Van Eijk RP, Heggie S, Thorpe KA, Ceslis A, et al. Hypermetabolism in ALS is associated with greater functional decline and shorter survival. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(10):1016–1023.

[119] He J, Fu J, Zhao W, Ren C, Liu P, Chen L, et al. Hypermetabolism associated with worse prognosis of amyotrophic lateral sclerosis. Journal of Neurology. 2022;269(3):1447–1455.

[120] Jésus P, Fayemendy P, Nicol M, Lautrette G, Sourisseau H, Preux PM, et al. Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral sclerosis. European Journal of Neurology. 2018;25(1):97–104.

[121] Desport JC, Preux PM, Magy L, Boirie Y, Vallat JM, Beaufrère B, et al. Factors correlated with hypermetabolism in patients with amyotrophic lateral sclerosis. The American journal of clinical nutrition. 2001;74(3):328–334.

[122] Desport JC, Torny F, Lacoste M, Preux PM, Couratier P. Hypermetabolism in ALS: correlations with clinical and paraclinical parameters. Neurodegenerative Diseases. 2005;2(3-4):202–207.

[123] Bouteloup C, Desport JC, Clavelou P, Guy N, Derumeaux-Burel H, Ferrier A, et al. Hypermetabolism in ALS patients: an early and persistent phenomenon. Journal of neurology. 2009;256(8):1236–1242.

[124] Hinault T, Segobin S, Benbrika S, Carluer L, Doidy F, Eustache F, et al. Longitudinal grey matter and metabolic contributions to cognitive changes in amyotrophic lateral sclerosis. Brain Communications. 2022;4(5):fcac228.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[125] Buhour MS, Doidy F, Mondou A, Pélerin A, Carluer L, Eustache F, et al. Voxel-based mapping of grey matter volume and glucose metabolism profiles in amyotrophic lateral sclerosis. EJNMMI research. 2017;7(1):1–11.

[126] Canosa A, Calvo A, Moglia C, Manera U, Vasta R, Di Pede F, et al. Brain metabolic changes across King's stages in amyotrophic lateral sclerosis: a 18F-2-fluoro-2-deoxy-d-glucose-positron emission tomography study. European journal of nuclear medicine and molecular imaging. 2021;48(4):1124–1133.

[127] Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Förstl H, et al. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiology of aging. 2007;28(1):42–50.

[128] Fukai M, Hirosawa T, Kikuchi M, Hino S, Kitamura T, Ouchi Y, et al. Different patterns of glucose hypometabolism underlie functional decline in frontotemporal dementia and Alzheimer's disease: FDG-PET study. Neuropsychiatry. 2018;8(2):441–447.

[129] Bejanin A, Tammewar G, Marx G, Cobigo Y, Iaccarino L, Kornak J, et al. Longitudinal structural and metabolic changes in frontotemporal dementia. Neurology. 2020;95(2):e140–e154.

[130] Schroeter ML, Vogt B, Frisch S, Becker G, Seese A, Barthel H, et al. Dissociating behavioral disorders in early dementia-an FDG-PET study. Psychiatry Research: Neuroimaging. 2011;194(3):235–244.

[131] Morbelli S, Ferrara M, Fiz F, Dessi B, Arnaldi D, Picco A, et al. Mapping brain morphological and functional conversion patterns in predementia late-onset bvFTD. European journal of nuclear medicine and molecular imaging. 2016;43(7):1337–1347.

[132] Liu YJ, Ju TC, Chen HM, Jang YS, Lee LM, Lai HL, et al. Activation of AMP-activated protein kinase $\alpha 1$ mediates mislocalization of TDP-43 in amyotrophic lateral sclerosis. Human molecular genetics. 2015;24(3):787–801.

[133] Liu YJ, Lee LM, Lai HL, Chern Y. Aberrant activation of AMP-activated protein kinase contributes to the abnormal distribution of HuR in amyotrophic lateral sclerosis. FEBS letters. 2015;589(4):432–439.

[134] Chida K, Sakamaki S, Takasu T. Alteration in autonomic function and cardiovascular regulation in amyotrophic lateral sclerosis. Journal of neurology. 1989;236(3):127–130.

[135] Shindo K, Tsunoda S, Shiozawa Z. Microneurographic analysis of muscle sympathetic nerve activity in amyotrophic lateral sclerosis. Clinical Autonomic Research. 1993;3(2):131–135.

[136] Tanaka Y, Yamada M, Koumura A, Sakurai T, Hayashi Y, Kimura A, et al. Cardiac sympathetic function in the patients with amyotrophic lateral sclerosis: analysis using cardiac [123I] MIBG scintigraphy. Journal of neurology. 2013;260(9):2380–2386.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[137] Merico A, Cavinato M. Autonomic dysfunction in the early stage of ALS with bulbar involvement. Amyotrophic Lateral Sclerosis. 2011;12(5):363–367.

[138] Pavlovic S, Stevic Z, Milovanovic B, Milicic B, Rakocevic-Stojanovic V, Lavrnic D, et al. Impairment of cardiac autonomic control in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2010;11(3):272–276.

[139] Takuma H, Kwak S, Yoshizawa T, Kanazawa I. Reduction of GluR2 RNA editing, a molecular change that increases calcium influx through AMPA receptors, selective in the spinal ventral gray of patients with amyotrophic lateral sclerosis. Annals of neurology. 1999;46(6):806–815.

[140] Shindo K, Tsunoda Si, Shiozawa Z. Increased sympathetic outflow to muscles in patients with amyotrophic lateral sclerosis: a comparison with other neuromuscular patients. Journal of the neurological sciences. 1995;134(1-2):57–60.

[141] Shindo K, Miwa M, Kobayashi F, Nagasaka T, Takiyama Y. Muscle sympathetic nerve activity in frontotemporal lobar degeneration is similar to amyotrophic lateral sclerosis. Clinical Autonomic Research. 2016;26(1):1–5.

[142] Kasarskis EJ, Berryman S, Vanderleest JG, Schneider AR, McClain CJ. Nutritional status of patients with amyotrophic lateral sclerosis: relation to the proximity of death. The American journal of clinical nutrition. 1996;63(1):130–137.

[143] van Mantgem MRJ, van Eijk RP, van der Burgh HK, Tan HH, Westeneng HJ, van Es MA, et al. Prognostic value of weight loss in patients with amyotrophic lateral sclerosis: A population-based study. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(8):867–875.

[144] Moglia C, Calvo A, Grassano M, Canosa A, Manera U, D'Ovidio F, et al. Early weight loss in amyotrophic lateral sclerosis: outcome relevance and clinical correlates in a population-based cohort. Journal of Neurology, Neurosurgery & Psychiatry. 2019;90(6):666–673.

[145] Saccà F, Quarantelli M, Rinaldi C, Tucci T, Piro R, Perrotta G, et al. A randomized controlled clinical trial of growth hormone in amyotrophic lateral sclerosis: clinical, neuroimaging, and hormonal results. Journal of neurology. 2012;259(1):132–138.

[146] Hubbard R, Will A, Peterson G, Sanchez A, Gillan W, Tan S. Elevated plasma glucagon in amyotrophic lateral sclerosis. Neurology. 1992;42(8):1532–1532.

[147] Patacchioli FR, Monnazzi P, Scontrini A, Tremante E, Caridi I, Brunetti E, et al. Adrenal dysregulation in amyotrophic lateral sclerosis. Journal of endocrinological investigation. 2003;26(12):RC23–RC25.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[148] Gargiulo Monachelli G, Meyer M, Rodríguez G, Garay L, Sica R, De Nicola A, et al. Endogenous progesterone is associated to amyotrophic lateral sclerosis prognostic factors. Acta neurologica scandinavica. 2011;123(1):60–67.

[149] Spataro R, Volanti P, Vitale F, Meli F, Colletti T, Di Natale A, et al. Plasma cortisol level in amyotrophic lateral sclerosis. Journal of the neurological sciences. 2015;358(1-2):282–286.

[150] Fang F, Hållmarker U, James S, Ingre C, Michaëlsson K, Ahlbom A, et al. Amyotrophic lateral sclerosis among cross-country skiers in Sweden. European journal of epidemiology. 2016;31(3):247–253.

[151] Daneshvar DH, Mez J, Alosco ML, Baucom ZH, Mahar I, Baugh CM, et al. Incidence of and mortality from amyotrophic lateral sclerosis in National Football League athletes. JAMA network open. 2021;4(12):e2138801–e2138801.

[152] Okouchi M, Okayama N, Steven Alexander J, Yee Aw T. NRF2-dependent glutamate-L-cysteine ligase catalytic subunit expression mediates insulin protection against hyperglycemia-induced brain endothelial cell apoptosis. Current neurovascular research. 2006;3(4):249–261.

[153] Duarte AI, Santos MS, Oliveira CR, Rego AC. Insulin neuroprotection against oxidative stress in cortical neurons–involvement of uric acid and glutathione antioxidant defenses. Free Radical Biology and Medicine. 2005;39(7):876–889.

[154] Bayunova L, Zorina I, Zakharova I, Avrova N. Insulin increases viability of neurons in rat cerebral cortex and normalizes Bax/Bcl-2 ratio under conditions of oxidative stress. Bulletin of Experimental Biology and Medicine. 2018;165(1):14–17.

[155] van Niekerk G, Christowitz C, Conradie D, Engelbrecht AM. Insulin as an immunomodulatory hormone. Cytokine & Growth Factor Reviews. 2020;52:34–44.

[156] Brunetta HS, Holloway GP. A theoretical argument to support the biological benefits for insulin stimulating mitochondrial oxidative phosphorylation. Current Opinion in Physiology. 2022;p. 100491.

[157] Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. Proceedings of the National Academy of Sciences. 2003;100(13):7996–8001.

[158] Ferrario CR, Reagan LP. Insulin-mediated synaptic plasticity in the CNS: Anatomical, functional and temporal contexts. Neuropharmacology. 2018;136:182–191.

[159] Zemel MB. Nutritional and endocrine modulation of intracellular calcium: implications in obesity, insulin resistance and hypertension. Molecular and Cellular Effects of Nutrition on Disease Processes. 1998;p. 129–136.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[160] Fredersdorf S, Thumann C, Zimmermann WH, Vetter R, Graf T, Luchner A, et al. Increased myocardial SERCA expression in early type 2 diabetes mellitus is insulin dependent: In vivo and in vitro data. Cardiovascular diabetology. 2012;11(1):1–11.

[161] Kahn AM, Allen JC, Seidel CL, Song T. Protein kinase C mediates insulin-inhibited Ca2+ transport and contraction of vascular smooth muscle. American journal of hypertension. 2000;13(4):383–388.

[162] O'Malley D, Harvey J. MAPK-dependent actin cytoskeletal reorganization underlies BK channel activation by insulin. European J Neurosci. 2007;25(3):673–682.

[163] Kahn AM, Seidel CL, Allen JC, O'Neil RG, Shelat H, Song T. Insulin reduces contraction and intracellular calcium concentration in vascular smooth muscle. Hypertension. 1993;22(5):735–742.

[164] Maimaiti S, Frazier HN, Anderson KL, Ghoweri AO, Brewer LD, Porter NM, et al. Novel calcium-related targets of insulin in hippocampal neurons. Neuroscience. 2017;364:130.

[165] Mankad P, James A, Siriwardena AK, Elliott AC, Bruce JI. Insulin protects pancreatic acinar cells from cytosolic calcium overload and inhibition of plasma membrane calcium pump. Journal of Biological Chemistry. 2012;287(3):1823–1836.

[166] Huang TJ, Price SA, Chilton L, Calcutt NA, Tomlinson DR, Verkhratsky A, et al. Insulin prevents depolarization of the mitochondrial inner membrane in sensory neurons of type 1 diabetic rats in the presence of sustained hyperglycemia. Diabetes. 2003;52(8):2129–2136.

[167] Whelan SA, Lane MD, Hart GW. Regulation of the O-linked β-N-acetylglucosamine transferase by insulin signaling. Journal of Biological Chemistry. 2008;283(31):21411–21417.

[168] Nagy T, Champattanachai V, Marchase RB, Chatham JC. Glucosamine inhibits angiotensin II-induced cytoplasmic Ca2+ elevation in neonatal cardiomyocytes via protein-associated O-linked N-acetylglucosamine. American Journal of Physiology-Cell Physiology. 2006;290(1):C57–C65.

[169] Ngoh GA, Watson LJ, Facundo HT, Jones SP. Augmented O-GlcNAc signaling attenuates oxidative stress and calcium overload in cardiomyocytes. Amino acids. 2011;40(3):895–911.

[170] Candé C, Vahsen N, Métivier D, Tourrière H, Chebli K, Garrido C, et al. Regulation of cytoplasmic stress granules by apoptosis-inducing factor. Journal of cell science. 2004;117(19):4461–4468.

[171] Pomytkin I, Krasilnikova I, Bakaeva Z, Surin A, Pinelis V. Excitotoxic glutamate causes neuronal insulin resistance by inhibiting insulin receptor/Akt/mTOR pathway. Molecular brain. 2019;12(1):1–4.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[172] McCarty MF. PKC-mediated modulation of L-type calcium channels may contribute to fat-induced insulin resistance. Medical hypotheses. 2006;66(4):824–831.

[173] Hoehn KL, Salmon AB, Hohnen-Behrens C, Turner N, Hoy AJ, Maghzal GJ, et al. Insulin resistance is a cellular antioxidant defense mechanism. Proceedings of the National Academy of Sciences. 2009;106(42):17787–17792.

[174] Fazakerley DJ, Chaudhuri R, Yang P, Maghzal GJ, Thomas KC, Krycer JR, et al. Mitochondrial CoQ deficiency is a common driver of mitochondrial oxidants and insulin resistance. Elife. 2018;7:e32111.

[175] Riahi Y, Israeli T, Cerasi E, Leibowitz G. Effects of proinsulin misfolding on β-cell dynamics, differentiation and function in diabetes. Diabetes, Obesity and Metabolism. 2018;20:95–103.

[176] Harding HP, Zeng H, Zhang Y, Jungries R, Chung P, Plesken H, et al. Diabetes mellitus and exocrine pancreatic dysfunction in perk-/- mice reveals a role for translational control in secretory cell survival. Molecular cell. 2001;7(6):1153–1163.

[177] Lipson KL, Fonseca SG, Ishigaki S, Nguyen LX, Foss E, Bortell R, et al. Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1. Cell metabolism. 2006;4(3):245–254.

[178] Pomytkin I, Pinelis V. Brain insulin resistance: Focus on insulin receptor-mitochondria interactions. Life. 2021;11(3):262.

[179] Wang CH, Wei YH. Role of mitochondrial dysfunction and dysregulation of Ca2+ homeostasis in the pathophysiology of insulin resistance and type 2 diabetes. Journal of Biomedical Science. 2017;24(1):1–11.

[180] James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nature Reviews Molecular Cell Biology. 2021;22(11):751–771.

[181] Taddeo E, Laker R, Breen D, Akhtar Y, Kenwood B, Liao J, et al. Opening of the mitochondrial permeability transition pore links mitochondrial dysfunction to insulin resistance in skeletal muscle. Molecular metabolism. 2014;3(2):124–134.

[182] Zarain-Herzberg A, García-Rivas G, Estrada-Avilés R. Regulation of SERCA pumps expression in diabetes. Cell Calcium. 2014;56(5):302–310.

[183] Uryash A, Mijares A, Lopez CE, Adams JA, Lopez JR. Chronic Elevation of Skeletal Muscle Ca2+i Impairs Glucose Uptake. An in Vivo and in Vitro Study. Frontiers in Physiology. 2022;p. 775.

[184] Yu J, Shi Y, Zhao K, Yang G, Yu L, Li Y, et al. Enhanced expression of β cell CaV3. 1 channels impairs insulin release and glucose homeostasis. Proceedings of the National Academy of Sciences. 2020;117(1):448–453.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[185] Mariosa D, Kamel F, Bellocco R, Ronnevi LO, Almqvist C, Larsson H, et al. Antidiabetics, statins and the risk of amyotrophic lateral sclerosis. European journal of neurology. 2020;27(6):1010–1016.

[186] Hu N, Ji H. Medications on hypertension, hyperlipidemia, diabetes, and risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. Neurological Sciences. 2022;p. 1–11.

[187] Pfeiffer RM, Mayer B, Kuncl RW, Check DP, Cahoon EK, Rivera DR, et al. Identifying potential targets for prevention and treatment of amyotrophic lateral sclerosis based on a screen of medicare prescription drugs. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2020;21(3-4):235–245.

[188] Dupuis L, Dengler R, Heneka MT, Meyer T, Zierz S, Kassubek J, et al. A randomized, double blind, placebo-controlled trial of pioglitazone in combination with riluzole in amyotrophic lateral sclerosis. PloS one. 2012;7(6):e37885.

[189] Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obesity reviews. 2010;11(1):11–18.

[190] De Tata V. Age-related impairment of pancreatic beta-cell function: pathophysiological and cellular mechanisms. Frontiers in Endocrinology. 2014;5:138.

[191] Frazier HN, Ghoweri AO, Anderson KL, Lin RL, Porter NM, Thibault O. Broadening the definition of brain insulin resistance in aging and Alzheimer's disease. Experimental neurol. 2019;313:79–87.

[192] Mariosa D, Hammar N, Malmström H, Ingre C, Jungner I, Ye W, et al. Blood biomarkers of carbohydrate, lipid, and apolipoprotein metabolisms and risk of amyotrophic lateral sclerosis: a more than 20-year follow-up of the Swedish AMORIS cohort. Annals of neurology. 2017;81(5):718–728.

[193] Dardiotis E, Siokas V, Sokratous M, Tsouris Z, Aloizou AM, Florou D, et al. Body mass index and survival from amyotrophic lateral sclerosis: a meta-analysis. Neurology: Clinical Practice. 2018;8(5):437–444.

[194] Peter RS, Rosenbohm A, Dupuis L, Brehme T, Kassubek J, Rothenbacher D, et al. Life course body mass index and risk and prognosis of amyotrophic lateral sclerosis: results from the ALS registry Swabia. European journal of epidemiology. 2017;32(10):901–908.

[195] Goutman SA, Boss J, Iyer G, Habra H, Savelieff MG, Karnovsky A, et al. Body mass index associates with amyotrophic lateral sclerosis survival and metabolomic profiles. Muscle & Nerve. 2022;.

[196] Lindauer E, Dupuis L, Müller HP, Neumann H, Ludolph AC, Kassubek J. Adipose tissue distribution predicts survival in amyotrophic lateral sclerosis. PloS one. 2013;8(6):e67783.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[197] Nau KL, Bromberg MB, Forshew DA, Katch VL. Individuals with amyotrophic lateral sclerosis are in caloric balance despite losses in mass. Journal of the neurological sciences. 1995;129:47–49.

[198] Marin B, Desport JC, Kajeu P, Jésus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. Journal of Neurology, Neurosurgery & Psychiatry. 2011;82(6):628–634.

[199] de la Rubia Ortí JE, Armero JLP, Sanchis-Sanchis CE, Sancho-Castillo S, Salazar A, Caplliure-Llopis J, et al. Muscle Function Differences between Patients with Bulbar and Spinal Onset Amyotrophic Lateral Sclerosis. Does It Depend on Peripheral Glucose? Journal of Clinical Medicine. 2021;10(8):1582.

[200] Brewer LD, Dowling AL, Curran-Rauhut MA, Landfield PW, Porter NM, Blalock EM. Estradiol reverses a calcium-related biomarker of brain aging in female rats. Journal of Neuroscience. 2009;29(19):6058–6067.

[201] Wold LE, Dutta K, Mason MM, Ren J, Cala SE, Schwanke ML, et al. Impaired SERCA function contributes to cardiomyocyte dysfunction in insulin resistant rats. Journal of molecular and cellular cardiology. 2005;39(2):297–307.

[202] Ozcan L, De Souza JC, Harari AA, Backs J, Olson EN, Tabas I. Activation of calcium/calmodulin-dependent protein kinase II in obesity mediates suppression of hepatic insulin signaling. Cell metabolism. 2013;18(6):803–815.

[203] American Diabetes Association Professional Practice Committee. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2022. Diabetes Care. 2022;45(Supplement_1):S125–S143.

[204] Wills AM, Hubbard J, Macklin EA, Glass J, Tandan R, Simpson EP, et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. The Lancet. 2014;383(9934):2065–2072.

[205] Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. The Journal of clinical investigation. 2001;108(8):1167–1174.

[206] Kaneb HM, Sharp PS, Rahmani-Kondori N, Wells DJ. Metformin treatment has no beneficial effect in a dose-response survival study in the SOD1G93A mouse model of ALS and is harmful in female mice. PloS one. 2011;6(10360):e24189.

[207] Cui C, Sun J, McKay KA, Ingre C, Fang F. Medication use and risk of amyotrophic lateral sclerosis-a systematic review. BMC medicine. 2022;20(1):1–23.

[208] Ziv I, Achiron A, Djaldetti R, Abraham M, Melamed E. Can nimodipine affect progression of motor neuron disease? A double-blind pilot study. Clinical neuropharmacology. 1994;17(5):423–428.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 January 2023 doi:10.20944/preprints202212.0297.v3

[209] Miller RG, Shepherd R, Dao H, Khramstov A, Mendoza M, Graves J, et al. Controlled trial of nimodipine in amyotrophic lateral sclerosis. Neuromuscular Disorders. 1996;6(2):101–104.

[210] Ovalle F, Grimes T, Xu G, Patel AJ, Grayson TB, Thielen LA, et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nature medicine. 2018;24(8):1108–1112.

[211] Secnik J, Cermakova P, Fereshtehnejad SM, Dannberg P, Johnell K, Fastbom J, et al. Diabetes in a large dementia cohort: clinical characteristics and treatment from the Swedish dementia registry. Diabetes care. 2017;40(9):1159–1166.

[212] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol. 2018;14(3):168–181.

[213] de la Monte SM, Tong M, Wands JR. The 20-year voyage aboard the journal of Alzheimer's disease: docking at 'Type 3 Diabetes', environmental/exposure factors, pathogenic mechanisms, and potential treatments. Journal of Alzheimer's Disease. 2018;62(3):1381–1390.

[214] Golimstok A, Cámpora N, Rojas JI, Fernandez MC, Elizondo C, Soriano E, et al. Cardiovascular risk factors and frontotemporal dementia: a case–control study. Translational neurodegeneration. 2014;3(1):1–6.

List of Abbreviations

ALS: amyotrophic lateral sclerosis.
AMPK: AMP-activated protein kinase.
ATP: adenosine triphosphate.
BMI: body mass index.
CRR: counter-regulatory response.
CSF: cerebrospinal fluid.
DB: diabetes mellitus.
DB1, DB2: type 1, type 2 diabetes mellitus.
ER: endoplasmic reticulum.
fALS: familial ALS.
FDA: food and drug administration.
FTD: frontotemporal dementia.
GLP-1: glucagon-like peptide 1.
Glut4: glucose transporter type 4.
GSH: glutathione.
H2O2: hydrogen peroxide.
HCD: hypercaloric carb diet.

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IIGU: insulin-independent glucose uptake.
IR: insulin resistance.
MTN: motor neuron.
OGTT: oral glucose tolerance test.
sALS: sporadic ALS.
SOD: superoxide dismutase.
TDP-43: TAR DNA-binding protein 43.